In the specification:

Please insert the following paragraph at Page 15 line 15:

--The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee. –

Please amend the paragraph beginning on page 15, line 28 – page 16, line 17 as follows:

FIGs. 1A-B are graphic representations of the differences in PMBC gene expression between MS patients and healthy subjects. RNA from Peripheral Blood Mononuclear Cells (PMBC) of 26 patients diagnosed with MS, and 18 healthy, age-matched controls was purified, labeled hybridized to a high density oligonucleotide array (~~Genechip~~ GENECHIP™) array (U95Av2, Affymetrix Inc. Santa Clara CA, USA), scanned and analyzed according to manufacturer's recommendations. The data were normalized and fold ratios calculated for each gene of the MS samples against the geometric mean of the controls. Figure 1A shows the number of MS specific genes detected having increased expression (fold change greater than 1.5) analyzed by t-test (red line), TNoM (green line) and INFO (blue line), compared with random occurrence (black line), at confidence levels (False Discovery Rates, FDR) of 90% (p= 0.10) to 100% (p= 0). Note the high level of significant MS-related gene expression at 95% FDR and above (arrows) (1249 distinguished genes). Figure 1B is an infogram of the 1249 genes most significantly (p<0.05 on all three tests) distinguishing MS patients (MS) from (control) healthy controls, determined as above. Each spot represents expression of a specific gene; color intensity of overexpressed (green) and under-expressed (red) genes indicates fold increase as compared to controls. Gray color indicates genes showing no difference in expression between MS and controls.

Please amend the paragraph on page 19, lines 3 – 26 as follows:

The profiles of MS-related genetic markers listed in Table I represent genes exhibiting differential expression in PBMCs from a large sample of MS patients, compared to that of age-matched healthy controls. Abundance of specific gene transcripts, represented by the intensity of label hybridizing to individual sequence loci of the MicroArray (Affymetrix Inc, Santa Clara CA), was recorded and quantified according to the manufacturers recommended protocols (such as high density oligonucleotide array (GENECHIP™)~~GeneChip~~ 3.0 software from Affymetrix). However, rather than composing the profile of differentially expressed genes based on probabilities using simple distribution of mean intensities, as has been reported by Ramanathan et al (J Immunol 2001;116:213-219), informative genes were selected based on the degree to which they were predictive of classification of the sample as "diseased" or "not diseased". By applying the rigorous three-pronged statistical analysis described in detail hereinbelow, 1249 genes most informative in distinguishing between diseased and otherwise not diseased patients were identified (see Table I). By applying an even more restrictive analysis of the data in Table I (see Table II, Bonfferoni analysis), a subset of the 300 highest scoring genes was identified. These MS marker genes comprise both over-expressed and downregulated genes, and represent of a diverse group of functional gene categories. Additional analysis of the markers uncovered herein also led to the identification of another restricted marker set which can be accurately utilized to diagnose probable MS patients. As is further described hereinbelow, the identification of such a marker set represents a significant breakthrough since it enables to treat individuals at a much earlier stage of MS then previously possible.

Please amend the paragraphs on page 20, line 28 – page 21, line 27 as follows:

As is detailed in the Examples section below, analysis of PBMC genes differentially expressed in MS, according to the methods described herein, revealed groups of genes of specific interest in MS. Genes that are most significantly over expressed, or downregulated in MS can indicate members of pathways important to disease development or pathology. Strongly overexpressed genes, according to Tables I and II, include SLAM (signaling lymphocyte activation molecule, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. U33017), LEF1 (lymphoid enhancer-binding factor 1, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. AL099409), LRP5 (low density lipoprotein receptor-related protein 5, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. AF077820), LILRB (leukocyte immunoglobulin-like receptor, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. AF004230), LY75 (lymphocyte antigen 75, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. AF011333), CDW52 (NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. N90866), PIP5K1-gamma (Phosphatidylinositol-4-phosphate 5-kinase, type 1, gamma, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. AB011161), MAP4 (Microtubule-associated protein 4, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. M64571), CTSK (Cathepsin K, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. X82153) and CTSB (Cathepsin B, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. L22507). Strongly down-regulated genes include IL1B (Interleukin 1 beta, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. M15330), TRAF6 (NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. U78798), SCYA20 (NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. U64197), IL1R (type1 receptor, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. M27492), IL1RAP

(receptor accessory protein, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. AB006537) and IL1RN (receptor antagonist, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. X52015), TGFB1 (Transforming growth Factor beta 1, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. X05839), SKI (v-ski sarcoma viral oncogene homologue, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. X15218), VEGF (Vascular endothelial growth factor, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. M63978), IGFBP4 (Insulin-like growth factor binding protein 4, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. U20982), EREG (epiregulin, NIH genetic sequence database, GENBANK~~GenBank~~ Accession No. NM_001432.1), and NR4A1, NR4A2, NR4A3 (nuclear receptor family genes, NIH genetic sequence database, GENBANK~~GenBank~~ Accession Nos. NM_002135.1, X75918 and U12767, respectively).

Please amend page 25, paragraph on line 18-25 as follows:

"Of particular importance is the marker set provided in Table V. As is described in the Examples section which follows, the present inventors also uncovered cellular markers which distinct between disease-related and non-disease related T-cell myelin reactivity (Table IV). Although MS appears to be caused by autoimmune T-cells activated against myelin self-antigens, myelin-reactive T-cells have been demonstrated in healthy subjects as well. Thus, distinction between disease-related and non-disease related T-cell myelin reactivity is of great clinical and investigational importance".

Please amend the paragraph on page 29, lines 3-17 to remove the embedded hyperlink as follows:

"The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. (J. Mol. Biol. 1990;215:403-10). BLAST nucleotide searches can be performed with the NBLAST program, score=100, wordlength=12 to obtain nucleotide sequences homologous to nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to marker protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) Nucleic Acids Res. 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See http://wwwdotncbidotnlmdotnihdotgov".

Please amend the paragraph on page 30, line 11 – Page 31, line 1 as follows:

In cases where detection involves discrete marker sets, the detection method of the present invention preferably employs marker probes which are conjugated to a solid support. For example, polynucleotide probes capable of specifically hybridizing with polynucleotide markers of the present invention (e.g., mRNA) may be coupled to an array (e.g., a high density oligonucleotide array (GENECHIP™)~~GeneChip~~ array for hybridization analysis), to a resin (e.g., a resin which can be packed into a column for column chromatography), or a matrix (e.g., a nitrocellulose matrix for northern blot analysis). The immobilization of molecules complementary to the marker(s), either covalently or noncovalently, permits a discrete analysis of the

presence or activity of each marker in a sample. In an array, for example, polynucleotides complementary to each member of a marker set may individually be attached to different, known locations on the array (region-specific arrays). The array may be hybridized with, for example, polynucleotides extracted from a blood sample obtained from a subject. The hybridization of polynucleotides extracted from the sample with the array at any location on the array can be detected, and thus the presence or quantity of the marker in the sample can be ascertained. In a preferred embodiment, a high density oligonucleotide array (GENECHIP™)~~"GeneChip"~~ array is employed (e.g., an Affymetrix type array). Similarly, Western analyses may be performed on immobilized antibodies specific for different polypeptide markers hybridized to a protein sample from a subject.

Please amend the paragraph on page 31, lines 8-13 to remove the embedded hyperlink as follows:

"Polynucleotide probes can be synthesized using any known synthesis method. Preferably, synthesis is effected using on-chip lithography methodology in a manner similar to that utilized for the synthesis of Affymetrix chips (wwwdotaffymetrixdotcom). Additional methods of array production and methodology are described in detail in the U.S. Patent Applications cited in the Background section hereinabove".

Please amend the paragraph on page 32, lines 17-24 to remove the embedded hyperlink as follows:

"The detection arrays described herein are preferably packaged in kits identified for use in detecting MS in general or for detecting specific stages of MS. The kit can further include reagents suitable for the detection of polynucleotide hybridization or antibody binding and instructions for effecting diagnosis using the kit components and suitable detection hardware (e.g., detection microscope) and

software (e.g., detection and analysis software). For further description of such hardware and software and detection reagents please see wwwdotaffymetrixdotcom".

Please amend the paragraphs on page 38, line 16 – page 39, line 28 as follows:

Microarray gene analysis *- Each high density oligonucleotide array (GENECHIP™) ~~Genechip~~ (U95Av2) which carries probes for 12,625 (or U133A with 22,000 for patients with probable MS diagnosis) transcripts was hybridized with 10µg/200µl hybridization mix, stained and scanned (Hewlett Packard, GeneArray-TM scanner G2500A) according to manufacturer protocol (Affymetrix Inc, Santa Clara, CA). Scaling procedure was performed to an average intensity of 600 per gene. A value of 20 was assigned to all measurements lower then 20. For comparison of healthy controls and MS patients, and between MS patients in acute relapse or remission: All data was normalized by dChip software and fold ratios were calculated for each gene of the samples against geometric means of the matched controls. For comparison of transcriptional profiles in MOG-reactive T-cells: Genes that did not have at least one average difference intensity value ≥100 or were present at least once by Affymetrix criteria, were not included in the analysis.*

Data analysis *- The analysis was performed according to the analytical approach as previously described (24-26). High density oligonucleotide array (GENECHIP™) ~~"GeneChip" Genechip~~ 4 software (Affymetrix Inc, Santa Clara, CA) was used for analysis of the scanned arrays. Fold ratios were calculated for each gene of the samples against the geometric mean of matched controls. For comparison of transcriptional profiles in MOG-reactive T-cells: To determine the most informative genes threshold number of misclassifications (TNoM) score was applied. This score counts the number of classification errors that occur between compared groups for each gene of the dataset. The best threshold (TNoM=0) implies that no errors have been counted and the distinction between the two groups in relation to the*

expression level of a specific gene is maximal. To select a group of strongly differential expression, t-test p-value (comparing expression levels of genes from MS patients vs. healthy controls) were also computed. Genes with TNoM = 0, fold-change >1.5 (either up or down regulated) and corresponded t-test P value < 0.05, were designated as most informative. For comparison of healthy controls and MS patients, and between MS patients in acute relapse or remission: The data was analyzed by the classic parametric t-test, and the following non-parametric tests: (i) Threshold number of misclassifications (TNoM) method and (ii) INFO score that measures the misclassifications made by a simple threshold in terms of the information lost. Analysis was performed between MS patients and the control group for each gene of the dataset as well as between subgroups of patients. Only informative MS related genes (p<0.05 in all three statistical tests) were included. To retrieve the most informative genes, the False Discovery Rate (FDR) method (14) that ranks and tests all "P" values against different thresholds was used. The degree of significance by the Bonferroni threshold method, which evaluates the allowed error probability divided by the number of genes measured, and ensures that each and every validated scoring event is indeed a significant event, was also calculated.

Please amend the paragraph on page 49 lines 12-18 as follows:

"Investigation of the known biological function of these genes (Table IV) shows a great diversity of activity (A Pie-chart diagram showing the functional groups of genes included in this evaluation is presented in Figure 3). Included are genes coding for proteins involved in the regulation and execution of apoptosis, growth factors, mediators of signal transduction pathways, molecules that participate in inflammation and also genes encoding heat shock proteins, transcription factors and components of different biochemical pathways".

Please amend page 49, paragraph on line 12-18 as follows:

"Investigation of the known biological function of these genes (Table IV) shows a great diversity of activity (A Pie-chart diagram showing the functional groups of genes included in this evaluation is presented in Figure 3). Included are genes coding for proteins involved in the regulation and execution of apoptosis, growth factors, mediators of signal transduction pathways, molecules that participate in inflammation and also genes encoding heat shock proteins, transcription factors and components of different biochemical pathways".

Please amend page 50, paragraph on lines 11-20 as follows:

"Downregulated Genes in MS-Derived T-cells - The profile of gene expression in MS-derived T-cells (Figure 4, and Table IV) indicates a suppression of apoptosis-related functions in the diseased state. One aspect of failure to induce apoptosis in the MS-derived T cell lines is the significant down-regulation of the gene encoding for the pro-apoptotic molecule TNF. A reduction in TNF could also contribute to a reduction in the ratio of pro- and anti-apoptotic transcript expression in the anti-MOG T cell lines from MS patients compared to healthy controls. Indeed, inadequate apoptosis present in MS autoreactive T cell lines could lead to insufficient deletion of autoimmune activated T cell clones and increase susceptibility to autoimmunity".

Please amend the paragraphs on page 114, line 10 – page 115, line 11 as follows:

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents, patent

applications ~~and sequences identifies by a GenBank accession number~~ mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent, patent application or sequence was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.